Reports

The Relations Between Cervical Cancer and Serological Markers of Nutritional Status

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Abstract

We evaluated whether differences in serological nutrient indicators between cases and controls were likely to be due to different usual levels for cases or to altered metabolism due to disease. Blood samples obtained as part of a case-control study of invasive cervical cancer conducted in Latin America were evaluated for case-control differences and for trends with stage of disease. Serum α- and β-carotene, cryptoxanthin, and α- and γ-tocopherol showed no trend with extent of disease, although Stage IV cases had lower α- and β-carotene values than did other cases. A slight trend of decreasing values with stage was observed for serum retinol, lycopene, and lutein. For cholesterol and triglyceride concentrations, an inverse trend was observed with stage of disease, which suggested a clinical effect of the disease on blood lipids. Adjustment for smoking, alcohol intake, or oral contraceptive use did not alter observed relations, nor was there evidence that the altered blood nutrient levels differed by histological type. These data suggest that serum values for some carotenoids from Stage I, II, and III cervical cancer are suitable for etiological studies, but spurious results may be obtained if late-stage cases are included. Evidence of trends with severity of disease for cholesterol and triglycerides, and possibly for retinol, lycopene, and lutein, suggest that special attention be given to disease effects of these nutrients in studies of cervical cancer.

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Introduction

Epidemiological studies often evaluate blood nutrient levels close in time to a diagnosis of cancer. Thus questions arise whether the blood levels reflect usual status for the individual, altered metabolism due to disease, medical workups or treatments, or altered eating habits due to illness. One strategy for evaluating these alternatives is to analyze blood samples periodically in prospective studies or to evaluate associations at various times after baseline blood collection. Another strategy is to observe blood levels across disease stages in cross-sectional studies using incident cases. Nutrient concentrations that are similar for all stages of disease but dissimilar to control levels favor the conclusion that these blood levels reflect usual status. Conversely, a trend in blood levels with stage of disease suggests that altered metabolism related to the disease process might be obscuring usual nutritional status.

Limited data are available regarding the effect of carcinogenesis on serum nutrient parameters, such as carotenoids, tocopherols, or retinol. The association of low cholesterol levels with various cancers, however, has received much attention for the past decade (1–6). For many cancer sites, associations seem attributable to metabolic disturbances related to the tumor, the so-called preclinical effect (3). Yet the effects of cervical cancer on serum cholesterol have not fallen into this category, inasmuch as lower levels may persist for many years before diagnosis (7–9). A case-control study of *in situ* disease showed increased risk with low cholesterol consistent with a preclinical disease effect or long-term low cholesterol concentrations (10). Results from one prospective study (11), however, are not consistent with these findings. Thus, studies are inconsistent with regard to the association of cholesterol values with cervical cancer, whereas disease effects have not been investigated for other nutritional parameters.

Epidemiological studies of cancer often restrict analyses to early-stage cases to minimize any disease effects and to exclude women who may be debilitated by the disease. With this in mind, we evaluated associations between serum micronutrients and case status in analyses restricted to early-stage cervical cancer cases (Stages I and II) and matched controls (12). New information from subjects with more advanced disease allows evaluation of risks associated with blood micronutrients and lipids among early- and late-stage cases and trends with stage of disease. In addition, availability of other risk factor data allowed evaluation of correlates of these serum parameters, inasmuch as it has been suggested that the observed lowered cholesterol may reflect other lifestyle factors (10).

Methods

The study methodology has been described in detail elsewhere (13,14). Briefly, newly diagnosed cases of invasive cervical cancer were ascertained from participating hospitals in four Latin American countries: Colombia, Costa Rica, Mexico, and Panama. Eligible cases were less than 70 years of age and had resided in the study areas for six months or more. Gynecological oncologists detected and staged 97.2% of cases in the study hospitals within each country according to the International Federation of Gynecology and Obstetrics. Histological information was available for 95.6% of the cases, the majority being of squamous or related histologies. All cases were pathologically confirmed as one of the following: papillary and squamous cell carcinomas, epithelial neoplasms (not otherwise specified), and basaloid carcinoma (International Classification of Diseases for Oncology 8010–8130). Two age-matched (5-yr group) hospital controls were selected for each case in Colombia and Mexico, and one hospital control and one community control were chosen for cases in Costa Rica and Panama. Hospital controls were randomly selected from admission lists from hospitals serving the geographic region of residence of the case. Patients with diseases known to be related to the exposures of interest in this study, particularly neoplastic, endocrine, nutritional, gynecological, or smoking-related diagnoses, were excluded. The disorders of hospital controls

were musculoskeletal, respiratory, infective, skin, or genitourinary (31%); digestive, principally abdominal hernia (21%); injuries or poisoning (14%); nervous system (14%); circulatory system, principally varicose veins (11%); and others (9%). Community controls resided in the same county as the case and were randomly selected from census listings. Replacement controls were selected for women who had undergone hysterectomy or had a history of cancer, whereas women who refused were not replaced.

The study was conducted between January 1986 and June 1987. Subjects were requested to complete an in-depth personal interview regarding a variety of factors including dietary intake of selected food items as well as demographic, reproductive, sexual, and medical histories. In addition, women were requested to undergo a pelvic examination and to donate a blood sample. A cervical swab was obtained from subjects to test for human papillomaviruses by filter *in situ* hybridization. Blood was drawn from cases and controls after the interview. Samples were drawn before treatment but coincident or close in time to hospitalization for cervical cancer cases, in a medical setting for hospital controls, and in clinics or at home for the community controls. Collected blood samples were transported in coolers, away from light, to the laboratory for processing. Participation rates were high, with 99% of cases and 96% of identified controls being interviewed, 96% of subjects providing cervical swabs, and 95% donating blood samples. Quality control procedures were incorporated to maintain standardization of the protocol across the field sites. A principal investigator or a study manager would visit each field site every three months to monitor interview and laboratory procedures, there were weekly telephone calls by the study manager to assess progress and manage problems, and there was a 10% reinterview of subjects to monitor quality of the study data.

Blood samples were collected without regard for time of day or fasting status. However, levels of retinyl palmitate suggest that over 90% of subjects were fasting at the time of collection. Samples were processed on the day of collection in a standardized fashion by uniformly trained laboratory personnel and were frozen locally. Once a month frozen samples were shipped to the United States to be maintained at −70°C for the duration of storage. Specimens were handled in a consistent fashion, except some samples for lipid analyses were stored in Costa Rica and Panama for several years. Thus, all late-stage cases (Stages III and IV) and matched controls were from Costa Rica and Panama (from Latin American storage), while early-stage cases (Stages I and II) and matched controls were from all four countries (from Latin American and U.S. repository storage). Lipid concentrations of early-stage cases and controls from U.S. storage did not differ from results for early-stage cases and controls from Latin American storage, suggesting no effect due to differential storage or thaws.

A standard high-performance liquid chromatography method (15) was used to evaluate levels of α-carotene, β-carotene, lycopene, lutein, cryptoxanthin, retinol, and α- and γ-tocopherol in the stored serum samples. Total cholesterol and triglycerides were determined using an automated clinical analyzer at the Centers for Disease Control.

Blood specimens were sent to the laboratory in batches over the course of two years for carotenoid and tocopherol analyses and over six months for lipid analyses. To monitor intralaboratory variation and possible drift with time, we inserted quality surveillance samples into daily batched samples as 10% of the total number of samples analyzed. Normal serum was used as quality surveillance pools at two levels for the carotenoids (low and normal) and for lipids (normal and high). Laboratory personnel were blinded to the quality control samples in their daily batches, although at baseline each laboratory ran each pool daily for 10 days to establish their own means and standard deviations. Periodic evaluation of Levy-Jenning plots of each carotenoid or lipid was performed by investigators external to the laboratory. Problems with analyses were discussed with laboratory personnel, and samples were reanalyzed as necessary. Coefficients of variation based on quality control samples ranged from 3.2% for α-tocopherol to 6.4% for β-carotene. All statistical analyses were performed using

SAS version 6.0. With the exception of retinol, we used the natural logarithm to transform all other nutrient values because of skewed distributions. Analysis of covariance was used to evaluate adjusted mean values between groups and to test trends with stage. Logistic regression was used to compare risk estimates of various stage groupings of cases with controls. Risk factors established previously in these data were included as potential confounders in these models (13,14). Serum cholesterol and triglycerides were added to micronutrient models to adjust for variable lipid concentrations. Trends in odds ratios (ORs) were evaluated by assigning ordinal values to the quartiles and using this continuous variable in the logistic models. Spearman correlation analyses were used to evaluate the association between serum nutrients and other risk factors.

Results

Older cases had more advanced disease (mean ages 42.5, 46.6, 50.0, and 51.8 yrs for Stages I, II, III, and IV, respectively). Therefore all subsequent analyses were adjusted for age.

Evaluation of serum micronutrient concentrations indicated some case-control differences and trends with stage (Table 1). Retinol levels were higher in controls than in cases as a group ($p = 0.002$), and later-stage cases (III + IV) tended to have lower concentrations than early-stage cases (I + II), suggestive of a trend. Lycopene and lutein also suggested a trend of lower values with more advanced disease, with the early-stage cases having values similar to those of the control group. Cases as a group had lower β- and α-carotene values than controls ($p < 0.001$ and $p = 0.004$, respectively), with no trends suggested with advancing disease, although values for Stage IV cases were somewhat lower than those for other cases. Concentrations of cryptoxanthin and α- and γ-tocopherol showed no relation with stage of disease, although case-control differences were observed ($p = 0.08$, 0.09, and 0.10, respectively). Of particular interest, cases had slightly higher γ-tocopherol values than controls; however, the previously noted increased risk with higher levels (12) is due to unusually high levels among Stage II cases. Because carotenoids and tocopherols are transported with serum lipoproteins, we standardized for variable lipid levels. However, adjustment for serum lipids did not alter the patterns shown in Table 1, with the exception of a diminished trend with stage for lycopene.

Cases had lower concentrations of cholesterol ($p = 0.007$) and triglycerides ($p = 0.04$) than controls and a trend of lower values with increasing stage of disease [p (trend) = 0.03 for both] (Table 2). Cholesterol concentrations among Stage I and II cases and triglyceride values among Stage I cases were similar to values among controls, whereas cases with more advanced disease had lower lipid concentrations. We evaluated whether the observed effects might be caused by the late-stage samples having been stored in Latin America, while the early-stage samples were stored in a variety of facilities. Analyses restricted to samples from early- and late-stage cases stored only in Latin America revealed a similar trend with stage for cholesterol and triglyceride values ($p = 0.003$ and 0.02, respectively). Some risk factors for cervical cancer may also be associated with nutrient levels and disease and, therefore, could explain the observed differences by case status. Likewise, an association with stage of disease could explain the trends with lipids. Many nutrients were associated with potential confounders, in the expected directions, such as current smokers having significantly lower β- and α-carotene and lycopene levels than nonsmokers among the controls ($p = 0.02$, 0.04, and 0.01, respectively); cholesterol concentrations were 161 and 169 mg/dl ($p = 0.01$) for never and ever oral contraceptive users, respectively, and 162 and 174 mg/dl ($p = 0.03$) for women reporting no alcohol and ≥48 g of alcohol per week, respectively. Controlling for smoking status, oral contraceptive use, and alcohol intake did not affect observed trends. Women with more advanced disease had slightly lower reported usual adult weight. Although weight differences were not statistically significant between stages, we examined the associations further, because this information was missing for up to 36% of women. Adjustment for adult body weight did

Table 1. Age-Adjusted Mean[a] (95% Confidence Interval) Serum Micronutrient Values[b] by Case-Control Status[c] and by Stage of Disease[d] for Four Latin American Countries

Group	*n*	Retinol	Lycopene	Lutein	β-Carotene	α-Carotene	Cryptoxanthin	α-Tocopherol	γ-Tocopherol
Controls	1,217	47.1 (46–48)	10.9 (10–11)	17.2 (17–18)	21.1 (20–22)	7.2 (7–8)	12.7 (12–13)	1,028 (1,011–1,046)	79 (77–82)
Cases	696	44.8 (44–46)	9.9 (9–11)	16.8 (16–18)	18.5 (18–20)	6.6 (6–7)	11.8 (11–13)	1,004 (982–1,027)	83 (80–88)
Stages									
I	167	48.2 (46–50)	12.5 (11–14)	17.5 (16–19)	18.9 (17–22)	6.7 (6–7)	12.0 (11–14)	991 (950–1,033)	77 (70–85)
II	220	46.6 (45–49)	10.4 (9–12)	18.0 (17–19)	19.4 (18–21)	6.9 (6–8)	11.3 (10–13)	1,019 (983–1,056)	102 (94–111)
III	277	41.3 (40–43)	8.4 (8–9)	15.9 (15–17)	18.1 (17–20)	6.6 (6–7)	11.8 (11–13)	1,003 (972–1,036)	76 (71–82)
IV	32	44.5 (39–50)	8.3 (6–11)	14.0 (12–17)	15.0 (12–19)	5.1 (4–6)	14.2 (11–19)	985 (897–1,081)	73 (58–91)

a: Nutrients are presented as untransformed values.
b: Values are μg/dl.
c: There are minor differences in number of subjects for some assays; missing data were due to laboratory problems and should not affect results.
d: Stage unknown for 9 cases.

Table 2. Age-Adjusted Mean (95% Confidence Interval) Serum Lipid Values[a] for Controls and Cervical Cancer Cases and by Stage of Disease

Group	*n*	Serum Nutrient, mg/dl	
		Cholesterol	Triglycerides
Controls	912	163 (160–165)	132 (128–137)
Cases	513	157 (154–160)	124 (119–131)
		Cases by stage[b]	
Stage I	151	160 (154–166)	134 (123–145)
Stage II	211	160 (155–165)	123 (115–131)
Stage III	128	151 (144–157)	116 (106–126)
Stage IV	14	148 (130–167)	119 (92–155)

a: Nutrients are presented as untransformed values.
b: Stage unknown for 9 cases.

not alter the micronutrient or lipid results across stage of disease, however. Of the other risk factors for disease identified in this study population, only interval since last Papanicolaou (Pap) test was correlated with stage of disease ($r = 0.19$). After adjustment for interval since last Pap test, the cholesterol and triglyceride inverse trends persisted, and trends with lipids were apparent among women who had received a recent Pap test and among those who had not.

Previous analyses of serum carotenoids, tocopherols, and retinol restricted to early-stage cancers and matched controls showed increased risk associated with low β-carotene and high γ-tocopherol (12). Inclusion of late-stage cancers and controls showed results similar to those of the early-stage cancers for β-carotene but diminished the elevated risks associated with γ-tocopherol levels. Comparison of the lowest quartile with increasing quartiles of γ-tocopherol showed ORs of 1.3, 1.8, and 2.1 among Stage I + II cases, whereas the ORs were 1.0, 1.4, and 1.4 when all cases were included in the analysis. For cholesterol, comparison of early-stage cases with controls revealed no consistent association with disease (Table 3), but evaluation of cases with more advanced disease showed a trend of lower risk with higher cholesterol values [p (trend) = 0.02]. Results were similar for triglyceride analyses; however, the reduced

Table 3. Odds Ratios[a] for Serum Lipids Restricted to Early- and Late-Stage Groupings

	Nutrient Quartiles[b]				*P* Trend Across Quartiles
	1 (Low)	2	3	4 (High)	
			Cholesterol		
Stages I and II	1.00 [101/224][c]	0.80 (0.6–1.2) [92/230]	1.04 (0.7–1.5) [100/231]	0.83 (0.6–1.2) [69/227]	0.68
Stages III and IV	1.00 [46/224]	0.84 (0.5–1.4) [42/230]	0.74 (0.4–1.3) [32/231]	0.48 (0.3–0.9) [22/227]	0.02
			Triglycerides		
Stages I and II	1.00 [95/227]	1.07 (0.7–1.6) [99/228]	1.02 (0.7–1.5) [98/221]	0.74 (0.5–1.1) [70/236]	0.15
Stages III and IV	1.00 [30/227]	1.65 (1.0–2.9) [59/228]	1.05 (0.6–1.9) [36/221]	0.55 (0.3–1.1) [17/236]	0.03

a: Adjusted for age, age at first intercourse, pregnancies, partners, interval since last Pap test, household facilities, human papillomaviruses.
b: Quartile cut points; cholesterol = 141, 165, and 193 mg/dl; triglycerides = 89, 131, and 203 mg/dl.
c: Nos. in brackets indicate number of cases/controls; 9 subjects with unknown stage were excluded.

risks were isolated to the fourth quartile in both stage groupings. Serum β-carotene, γ-tocopherol, and other risk factors did not explain the reduced risks associated with high serum lipid levels, nor did the lipids influence the findings for the micronutrients. Results limited to the community controls were similar to the findings for the overall group.

Adenocarcinomas and adenosquamous cell carcinomas are uncommon and may have risk factors different from the more common squamous types (16). Carotenoids, tocopherols, and retinol concentrations were similar between the squamous ($n = 615$) and adenocarcinoma/adenosquamous groups ($n = 53$). Cholesterol and triglyceride values were lower for cases with squamous tumors (157 and 125 mg/dl, respectively) than for controls (163 and 132 mg/dl, respectively). Although the adenocarcinoma/adenosquamous group had values intermediate between the other groups ($n = 38$, 160, and 130, respectively), adjustment for stage made values for the two tumor groups more comparable.

Discussion

Overall, no trends with stage were observed for cryptoxanthin and α- and γ-tocopherol. There was an indication of altered values among Stage IV cases for α- and β-carotene, suggesting that stage restriction would be beneficial for these nutrients. Retinol, lycopene, lutein, and blood lipids, however, showed relatively consistent trends with stage, suggesting that all cases may suffer from altered concentrations. There was no indication that adenosquamous and adenocarcinoma cell types differed from squamous with regard to nutrient levels, but limited size of the subgroup made interpretation difficult.

In general, results from previous studies do not support a preclinical lowering of cholesterol concentrations. Two prospective studies from the United States showed increased incidence of cervical cancer in the lowest-cholesterol group, even after subjects diagnosed within the first two years of follow-up were excluded (8,9). Data from one study (8) suggested that the lowered cholesterol may be present 10 years before the diagnosis of cervical cancer. Consistent with these findings, a case-control study showed low plasma cholesterol associated with a preinvasive cervical lesion (10). Interestingly, in our study, women with Stage I disease showed values only slightly lower than those of controls. In contrast to previous studies, a prospective study from Finland (11) showed increased relative risks of cervical cancer with high cholesterol concentrations, although elevated risks for other cancers were associated with low cholesterol concentrations. These findings persisted after exclusion of the first four years of follow-up.

This Latin American population had lower cholesterol concentrations than those studied previously (8,9,11), yet similar findings with regard to relative ranking were observed. The cut point for our highest quartile (>193 mg/dl) was close to those for the lowest or second lowest quintiles in U.S. cohorts [<185 mg/dl (8) and 180–203 mg/dl (9)] and the second highest quartile in the Australian study [193–232 mg/dl (10)]. Nonetheless, in these studies, the high-cholesterol group was found to be at reduced risk compared with the low-cholesterol group. These studies show risks related to the extremes of the distribution, particularly with relatively low levels represented (<180–200 mg/dl). Therefore the positive association noted in the Finnish cohort (11) could be due to the lack of a low-cholesterol group (lowest quintile ≤230 mg/dl).

In our study of invasive disease, cholesterol and triglyceride concentrations were lower at higher stages, suggesting a clinical disease effect on blood lipids. The metabolic determinants and correlates of these commonly measured blood parameters may have etiologic, diagnostic, or treatment significance. For example, some tumor cells have elevated low-density lipoprotein-receptor activity, which could account for the hypocholesterolemia (17). Buchwald (18) hypothesized that because some tumor cells seem to have a higher cholesterol requirement than normal cells, inhibition of cholesterol availability would limit tumor growth. Although there is speculation about the relevance of this preclinical/clinical cholesterol effect for some

tumors, no data specifically relevant to cervical neoplasia have emerged.

It has been postulated that the lowered cholesterol levels may reflect retinol or carotenoid levels (11,19). In our data, the risk of cervical cancer associated with lowered blood levels of lipids persisted after adjustment for carotenoids. In addition, other factors related to serum lipids did not explain the trends observed with stage of disease. The late-stage group in our study and data from one prospective study (9) showed linearly decreasing risk of cervical cancer as cholesterol levels increased, yet inconsistent trends were observed among our early-stage grouping and in two other studies (8,11). Our data suggest that merging early- and late-stage cancers would be inappropriate, and previous inconsistent trends may have resulted from large numbers of women with early-stage disease or perhaps confounding by unmeasured life-style factors.

Monitoring quality control throughout the study and correction of problems during the assay period gave us confidence in the laboratory values. Our evaluation of micronutrient and lipid concentrations among controls who consumed alcohol, smoked cigarettes, or used oral contraceptives was in agreement with expected associations (20–24). These evaluations of the data bolstered our confidence in the measurement of these nutritional parameters.

Despite a limited number of Stage IV cases, our analyses suggest that these women had altered α- and β-carotene concentrations compared with either controls or cases with less severe disease. Thus, inclusion of Stage I, II, and III cervical cancer cases seems appropriate for etiologic studies of these nutrients. The tocopherols and cryptoxanthin would not pose problems in case-control studies, although addition of Stage III cases to studies limited to early-stage cases can be informative, as evidenced by the γ-tocopherol results. The suggested trends in retinol, lycopene, and lutein seem problematic to case-control studies and suggest that restriction to early-stage cases would not be sufficient if nutrient levels of all cases were being affected by disease. Validation of these retinol, lycopene, and lutein findings in prospective data would be useful. Although the investigation of risk associated with cholesterol and triglycerides per se in case-control or cohort studies of cervical cancer is questionable, the biologic relevance of lowered cholesterol and triglyceride concentrations in the neoplastic process is curious and warrants closer scrutiny.

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